EXHIBIT 8

EXPERT REPORT OF MARK A. SCHUMACHER, M.D., Ph.D.

MARCH 25, 2019

opioids for a wide array of conditions beyond short-term acute pain, cancer pain from active disease, and end-of-life and hospice care.

6. The prevalence of chronic pain is a valid concern but should not be confused with underutilization of opioids. In addition, to the extent that there was some amount of under-treated pain, it does not follow that the best treatment then (or now) would have been an opioid; indeed, in the vast majority of cases the best treatment would have been something other than an opioid, and likely a combination of physical, pharmacologic, and behavioral approaches.

7. More specifically, I provide the following opinions based on my experience, review of academic literature, and review of documents and certain information produced in discovery in this action:

8. It is my opinion to a reasonable degree of certainty in the field of pain medicine that the medical standard of care for treating both chronic and acute pain was changed as a result of widespread promotion and marketing of opioids by Defendants[1] that trivialized the risk of addiction and exaggerated the benefits of long-term opioid use.

9. It is my opinion to a reasonable degree of certainty in the field of pain medicine that Defendants influenced physicians through direct-to-physician marketing, medical education, and industry-sponsored and -funded Key Opinion Leaders ("KOLs") to prescribe long-term opioids based on misinformation about the risks and benefits of chronic opioid use.

10. It is my opinion to a reasonable degree of certainty in the field of pain medicine that for the vast majority of chronic pain patients, the risks of prescription opioids significantly

[1] "Defendants" as used herein refers to the Defendant manufacturers of branded and generic opioid products in the actions brought by Plaintiffs Cuyahoga County and Summit County: Purdue Pharma, Endo, Janssen, Teva, Cephalon, Mallinckrodt, Actavis, and Allergan.

diminish or resolve. While opioids can provide effective immediate pain relief, they do not reverse the pathophysiologic states of chronic pain.

3. History of Opioid Use

27. Over the past 25 years the United States has experienced an unprecedented increase in opioid-use disorder (OUD, which is sometimes used interchangeably with "addiction"), opioid overdose, and other opioid-related harms. As of 2017, 2.1 million Americans aged 12 years or older had an OUD involving prescription opioids, and about 700,000 had an OUD involving heroin, an illicit opioid (HHS 2018). Drug overdose, driven primarily by opioids, is now the leading cause of unintentional injury death in the United States. Two out of three drug overdose deaths involve an opioid (Hedegaard H 2018). Overdose deaths from opioids have increased almost six times since 1999 (CDC 2018). Overdoses involving opioids killed more than 47,000 people in 2017, and 36% of those deaths involved prescription opioids (Scholl et al. 2018). This increase in opioid-related deaths has occurred in tandem with an equally unprecedented increase in the prescribing of opioid medications for purposes of pain management.

28. This latest chapter in the modern medical use of opioids in this country represents a significant departure from the one preceding it. Below I provide a brief outline of the historical context leading up to the current situation.

a. For centuries, doctors have known that opioids are one of the most potent analgesic agents available, but they have also known that opioids are highly addictive.

29. Opioids have been used for medicinal and recreational purposes for millennia. While the use of opioids for treatment of acute severe pain has generally been accepted, their use for managing chronic noncancer pain has been controversial since the 19th century, with the popular view shifting over the decades between broad acceptance versus a more restrictive

channels. This act had the effect of criminalizing the use of opium for nonmedical purposes (Courtwright 2015; Hoffman 2016). The use of heroin for medicinal and other purposes was specifically banned by the Heroin Act, enacted in 1924.

32. The consensus among medical professionals for most of the 20th century was that opioids should not be used for the management of chronic pain because of the lack of evidence regarding their effectiveness for this type of pain and the risk of addiction. For example, in a survey of physicians in the early 1970s, "when asked why they would not go higher [in dosing meperidine] if pain persisted, 40% of the doctors stated that higher doses were no more effective, with 60% stated that higher dosages contained the danger of serious side effects." (Marks and Sachar 1973) Some researchers even concluded that doctors were under-prescribing opioids due to an exaggerated fear of addiction (Morgan 1985). Research aimed at developing new and potentially less-addictive opioids continued. Nevertheless, Percocet (oxycodone) and Vicodin (hydrocodone) which combined semisynthetic opioids with acetaminophen, became available in the 1970s for relief of moderate to moderately severe pain. These and most other prescription opioids are now regulated under the Controlled Substances Act (CSA) of 1970 as Schedule II drugs—those with a "high potential for abuse which may lead to severe psychological or physical dependence" (DEA 2019).[2]

b. Increased opioid prescribing in 1990s for cancer and palliative care

33. The stigma associated with opioids meant that they often were not used or were used sparingly even for people with terminal cancer. American physicians worked to change this approach and expand the use of opioids for cancer and palliative care.

[2] Some opioids are not classified in Schedule II. These include opioids containing less than 90 milligrams of codeine per dosage unit (e.g., Tylenol with Codeine®) and buprenorphine (used in the treatment of OUD), which are Schedule III drugs—those with "a potential for abuse less than substances in Schedules I or II" and whose "abuse may lead to moderate or low physical dependence or high psychological dependence" (DEA, 2019).

OxyContin to the opioid most associated with cancer (morphine) or stating that OxyContin was a strong as morphine (when in fact the oxycodone is stronger).

49. In 1996, the American Academy of Pain Medicine and American Pain Society issued a joint consensus statement titled *The Use of Opioids for the Treatment of Chronic Pain*, describing potential benefits of using opioids for management of chronic pain (including non-cancer) (Haddox et al. 1997). This included statements that promoted the use of opioids for chronic non-cancer pain, that the risk of prescription opioids causing addiction was a myth, and chronic pain can be measured on a 0 to 10 scale as easily as acute pain (Campbell 1996). Moreover, it was argued by this group that studies indicate that the de novo development of addiction when opioids are used for the relief of pain is low and the risk of opioid-induced respiratory depression tends to be a short-lived phenomenon that generally occurs only in the opioid-naive patient, and is antagonized by pain (Haddox et al. 1997)—a dangerous position that was never grounded in rigorous science and has been proven wrong (Dowell, Haegerich, and Chou 2016).

50. There were also concerted efforts by pain specialists funded significantly by Purdue and the other opioid manufacturers to persuade state medical boards and state legislatures to remove legal impediments to opioid-based pain treatment (Hoffman 2016). This was accompanied by a campaign to call public and professional attention to the prevalence of pain and its seriousness as a public health problem. This concept was also supported by the American Academy of Pain Medicine and American Pain Society to advocate for the interests of pain patients suggesting that pain be considered a "5th vital sign," ostensibly in an effort to improve pain assessment and treatment. (Campbell 1996). Although increasing attention was drawn to the assessment and treatment of pain, there was little to no progress in the development of novel pain

warning letter to the manufacturer regarding promotional materials that omitted and minimized the drug's safety risks (FDA 2017).

53. Nonetheless, sales of prescription opioids continued to increase (Pan 2016). The increase in opioid prescribing that began during the 1990s was associated with a parallel increase in opioid-related substance use disorders and opioid-related deaths (Dowell, Haegerich, and Chou 2016; Kolodny et al. 2015). Using conservative estimates excluding non-methadone synthetics, prescription opioids overdoses accounted for 17,087 deaths in 2016, up from approximately 3,442 in 1999 (Seth et al. 2018). While there are indications that opioid prescribing is decreasing, as recently as 2017, tens of millions of opioids were dispensed in the U.S. (191 million total opioid prescriptions) (CDC 2017). Although recent data do show a leveling off in opioid prescribing, rates in the United States remain at historically high levels and substantially greater than the rates seen in other industrialized Western countries. These high prescribing rates continue despite the lack of evidence supporting such practices and the abundant evidence of the risks and harms of opioid use. The rates of prescription and illicit opioid misuse, a shift from prescription opioids to illicit markets, overdose, and admissions to drug treatment programs have all increased in parallel to burgeoning opioid prescribing (Rudd et al. 2016).

IV. DETAILED STATEMENT OF OPINIONS

54. This opioid crisis lies at the intersection of two substantial public health challenges: containing the rising toll of opioid-related harms and reducing the burden of suffering for the tens of millions of people suffering from pain. Finding the ideal balance is a challenge for all physicians and health care providers. While there are a number of reasons why the epidemic was able to take root in the Country—from the lack of medical education on the

treatment of pain, to the market forces that caused a decrease in the availability of multidisciplinary pain treatment—there is no real question that the epidemic has been driven by an unwarranted increase in prescription opioids orchestrated by the pharmaceutical industry. The total opioid prescribing rate more than doubled in the U.S. from 1995 to 2013 (IMS Health 1997-2013). This trend is confirmed by prescription data from 1995-2010 derived from the National Ambulatory Medical Care Survey showing a substantial increase in opioid prescriptions between 1995 and 2010 in office-based medical visits, especially in visits by middle-aged and older adults and by patients making their first visit to the treating physician (Olfson et al. 2013).

A. The medical standard of care for treating both chronic and acute pain was changed because of widespread promotion and marketing of opioids that trivialized the risk of addiction and exaggerated the benefits of long-term opioid use.

55. As part of our work on the NASEM Consensus Study Report, my colleagues and I relied on a traditional multi-factorial causal model commonly used in public health, ranging from structural factors to individual susceptibility. Using this approach, we found certain hypotheses about "causes" of the epidemic to be inescapable. Of particular note, data present a prima facie case that heavy promotion of opioid prescribing by Defendants (including misleading claims), substantially increased prescribing by physicians and was the key contributor to the increase in misuse, OUD, and accompanying harms. (Van Zee 2009; GAO 2003; Hoffman 2016; Cicero, Inciardi, and Munoz 2005; 'Vital signs: overdoses of prescription opioid pain relievers - United States, 1999-2008' 2011).

56. Opioid manufacturers took advantage of physicians' desire to provide relief to large population of people with chronic pain conditions. In 2016, the CDC estimated 50 million US adults suffer chronic pain, defined as reporting pain every day or most days over the past 6 months; and 19.6 million U.S. adults suffer from "high-impact chronic pain," defined as chronic pain that frequently limits life or work activities (Dahlhamer et al. 2018). The CDC explains:

"National estimates of high-impact chronic pain can help differentiate persons with limitations in major life domains, including work, social, recreational, and self-care activities from those who maintain normal life activities despite chronic pain, providing a better understanding of the population in need of pain services." (Dahlhamer et al. 2018) Chronic pain, however, is complex and difficult to treat.

57. While multidisciplinary pain treatment demonstrates substantial effectiveness, for the reasons discussed above, access to this type of treatment diminished in the 1990s. Yet, of course, physicians' desire to help their patients remained. It is, thus, particularly unfortunate from a public health perspective that it was at this precise moment that Purdue's unprecedented marketing campaign for OxyContin took shape (GAO 2003). It was fertile ground for a campaign based on the promise that these opioids were new and improved and specifically designed to provide effective relief for chronic pain with very low risk of addiction.

1. The campaign to persuade doctors to prescribe "new" opioids

58. In my opinion, the driving force of this national catastrophe has been the introduction and marketing of long-acting formulations of high potency opioids such as OxyContin beginning in 1996. Physicians were misled through Defendants' marketing and sales detailing intended to persuade doctors to accept that more potent and long-acting formulations of opioids (such as OxyContin) were safe and effective in the treatment of multiple forms of pain, especially chronic non-cancer pain, and even at high doses.

59. Purdue and other Defendants utilized a number of approaches to encourage physicians to prescribe opioids broadly for the treatment of chronic pain. They engaged in direct-to-consumer marketing. They marketed directly to physicians through sales representatives. They funded research, pain-related medical societies, and continuing medical education, lobbied medical boards and agencies responsible for pain-related treatment guidelines,

and lobbied state and local government to remove barriers to broader use of opioids for the treatment of pain. ('Fueling an epidemic. Exposing the financial ties between opioid manufacturers and third party advocacy groups' 2018). A common feature across all of these efforts to promote the broader use of opioids was the message that the risk of addiction was rare, and the benefits of long-term opioid use were well established. These efforts were remarkably successful:

> An in-depth analysis of the promotion and marketing of OxyContin (Purdue Pharma, Stamford, CT), a sustained-release oxycodone preparation, illustrates some of the key issues. … OxyContin's commercial success did not depend on the merits of the drug compared with other available opioid preparations. The *Medical Letter on Drugs and Therapeutics* concluded in 2001 that oxycodone offered no advantage over appropriate doses of other potent opioids. Randomized double-blind studies comparing OxyContin given every 12 hours with immediate-release oxycodone given 4 times daily showed comparable efficacy and safety for use with chronic back pain and cancer-related pain. … In 2001 alone, the company spent $200 million in an array of approaches to market and promote OxyContin.
>
> From 1996 to 2001, Purdue conducted more than 40 national pain-management and speaker-training conferences… Purdue promoted among primary care physicians a more liberal use of opioids, particularly sustained-release opioids. …
>
> Purdue's promotion of OxyContin for the treatment of non–cancer-related pain contributed to a nearly tenfold increase in OxyContin prescriptions for this type of pain, from about 670 000 in 1997 to about 6.2 million in 2002… Prospective, randomized, controlled trials lasting at least 4 weeks that evaluated the use of opioids for chronic, non–cancer-related pain showed no consistent improvement in physical functioning. …
>
> When OxyContin entered the market in 1996, the FDA approved its original label, which stated that iatrogenic addiction was "very rare" if opioids were legitimately used in the management of pain. In July 2001, to reflect the available scientific evidence, the label was modified to state that data were not available for establishing the true incidence of addiction in chronic-pain patients [and] also deleted the original statement that the delayed absorption of OxyContin was believed to reduce the abuse liability of the drug.
>
> …Purdue funded more than 20 000 pain-related educational programs through direct sponsorship or financial grants, providing a venue that had enormous influence on physicians' prescribing throughout the country.

(Van Zee 2009). Evidence I have reviewed, including Defendants' internal communications, sales representative training materials and call notes, and promotional materials supports Dr. Van Zee's conclusions. A number of examples of this information are attached to my report as Exhibits A-C. These examples are not intended to be exhaustive, but, rather, illustrative of the Defendants' actions.

60. It is my opinion that as a result of direct-to-consumer and direct-to-physician marketing, as well as other efforts by opioid manufacturers to promote the widespread and long-term use of opioids, that the risk of addiction was trivialized, and the benefits of long-term opioid use overstated. Physicians were influenced by these efforts and a cautious and conservative approach to the use of opioids for the treatment of pain was replaced with much more liberal prescribing practices. I observed this firsthand in my own training after emerging from residency in 1995 to find increasing use of more potent formulations of opioids and sustained-release opioids for acute and chronic noncancer pain.

2. Specific misstatements designed to encourage physicians to overcome their reluctance to prescribe opioids liberally for chronic pain

61. Opioid manufacturers promoted chronic use of opioids based upon a set of key misrepresentations. These included the following: (1) taking long-acting opioids as prescribed for pain protects against addiction and abuse; (2) that new opioid formulations had no ceiling dose and were safe at high doses; and that (3) chronic opioid therapy improves function and quality of life. These misrepresentations appeared in print promotional materials and were also repeated by sales representatives in their direct marketing to physicians. In addition, (4) Purdue, at OxyContin's launch, took advantage of and was careful to maintain the perception that oxycodone is less potent than morphine, when in fact it is more potent.

problem by casting doubt on the studies demonstrating increased risk, thereby creating more confusion and prolonging sales.

106. However, the risks associated with the use of prescription opioids are numerous and can be life-threatening. What factors have driven this? In the Washington State workers' compensation system, the total number of opioid prescriptions tripled between 1996 and 2002. However, prescriptions for the most potent opioids such as oxycodone (Schedule II), as a percentage of all scheduled opioid prescriptions (II, III, and IV), increased from 19.3% in 1996 to 37.2% in 2002. Among long-acting opioids, the average daily morphine equivalent dose increased by 50%, to 132 mg/day (Franklin et al. 2005). Franklin et al. found that as injured Washington workers were given more prescriptions of higher doses of opioids, the rates of opioid overdoses among that population jumped, from zero in 1996 to more than twenty in 2005. And in 2009, over thirty people receiving opioid prescriptions through the Workers' Compensation Program died of an opioid overdose.

107. Doctors wrote 72.4 opioid prescriptions per 100 persons in 2006. This rate increased 4.1% annually from 2006 to 2008 and 1.1% annually from 2008 to 2012. It then decreased reaching a rate of 66.5 per 100 persons in 2016. A record number of drug overdose deaths occurred in 2015: 52,404. While a death may involve more than one drug, prescription or illicit opioids were involved in 63.1% of these deaths. There was a steady increase in mortality rates for natural or semi-synthetic opioids (e.g., hydrocodone, oxycodone) from 1999 to 2010, but now has been replaced by climbing rates of heroin and especially synthetics such as fentanyl. For OD deaths involving synthetic opioids other than methadone, the rate increased from 0.3 per 100,000 in 1999 to 3.1 in 2015 ($p<0.05$) – a ten-fold increase (Annual Surveillance Report of

Drug-Related Risks and Outcomes. Centers for Disease Control and Prevention. https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf, 2017).

108. Risks of dependence and addiction are greater when opioid analgesics are used long-term than when they are used short-term (Boscarino et al. 2011). Moreover, it has been shown that once patients have been on opioids longer than 90 days, the risk that they will continue on opioids chronically and for developing a substance use disorder increase (Krashin, Murinova, and Sullivan 2016). In addition to substance use disorder (Han et al. 2017), morbidity related to opioid therapy for chronic pain includes reduced testosterone, cardiac abnormalities, fractures, and immunosuppression, among other adverse outcomes (Chou et al. 2015).

109. When randomized trials and observational studies involving adults with chronic pain who were prescribed long-term opioid therapy (opioid therapy evaluated long-term (>1 year) were examined, there was insufficient evidence to determine the effectiveness of long-term opioid therapy for improving chronic pain and function. However, an opioid dose-dependent risk for serious harms was found (Chou et al. 2015). In other patient populations (veterans) associations have also been established between occasional and chronic opioid use and increased risk of hospital readmission, and risk of death (Mosher et al. 2014). A retrospective population-based cohort study conducted of opioid prescriptions given to patients with polyneuropathy, long-term opioid therapy did not improve functional status but rather was associated with a higher risk of subsequent opioid dependency and overdose. (Hoffman et al. 2017).

110. In a national sample of 1,424 people across Australia experiencing pain for a median of 10 years, greater daily OME (oral morphine equivalent) consumption was associated with higher odds of multiple physical and mental health issues, aberrant opioid use, problems associated with opioid medication and opioid dependence. Past-year dependence was

DATED March 25, 2019.

Mark A. Schumacher, PhD, MD